University of Zurich[UZH]

Zurich Open Repository and Archive
University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2015

Drug-eluting stents vs. bare metal stents in patients with cardiogenic shock: a comparison by propensity score analysis

Jaguszewski, Milosz ; Ghadri, Jelena-Rima ; Seifert, Burkhardt ; Hiestand, Thierry ; Herrera, Paola ; Gaemperli, Oliver ; Landmesser, Ulf ; Maier, Willibald ; Nallamothu, Brahmajee K ; Windecker, Stephan ; Lüscher, Thomas F ; Templin, Christian

Abstract: BACKGROUND In patients with cardiogenic shock, data on the comparative safety and efficacy of drug-eluting stents (DESs) vs. bare metal stents (BMSs) are lacking. We sought to assess the performance of DESs compared with BMSs among patients with cardiogenic shock undergoing percutaneous coronary intervention (PCI). METHODS Out of 236 patients with acute coronary syndromes complicated by cardiogenic shock, 203 were included in the final analysis. The primary endpoint included death, and the secondary endpoint of major adverse cardiac and cerebrovascular events (MACCEs) included the composite of death, myocardial infarction, any repeat revascularization and stroke. Patients were followed for a minimum of 30 days and up to 4 years. As stent assignment was not random, we performed a propensity score analysis to minimize potential bias. RESULTS Among patients treated with DESs, there was a lower risk of the primary and secondary endpoints compared with BMSs at 30 days (29 vs. 56%, $P < 0.001$; 34 vs. 58%, $P = 0.001$, respectively) and during long-term follow-up [hazard ratio 0.43, 95% confidence interval (CI) 0.29-0.65, $P < 0.001$; hazard ratio 0.49, 95% CI 0.34-0.71, $P < 0.001$, respectively]. After propensity score adjustment, all-cause mortality was reduced among patients treated with DESs compared with BMSs both at 30 days [adjusted odds ratio (OR) 0.26, 95% CI 0.11-0.62; $P = 0.002$] and during long-term follow-up (adjusted hazard ratio 0.40, 95% CI 0.22-0.72; $P = 0.002$). The rate of MACCE was lower among patients treated with DESs compared with those treated with BMSs at 30 days (adjusted OR 0.42, 95% CI 0.19-0.95; $P = 0.036$). The difference in MACCEs between devices approached significance during long-term follow-up (adjusted hazard ratio 0.60, 95% CI 0.34-1.01; $P = 0.052$). CONCLUSION DESs appear to be associated with improved clinical outcomes, including a reduction in all-cause mortality compared with BMSs among patients undergoing PCI for cardiogenic shock, possibly because of a pacification of the infarct-related artery by anti-inflammatory drug. The results of this observational study require confirmation in an appropriately powered randomized trial.

DOI: https://doi.org/10.2459/JCM.0000000000000106

Posted at the Zurich Open Repository and Archive, University of Zurich
ZORA URL: https://doi.org/10.5167/uzh-98111
Journal Article
Published Version

Originally published at:
Jaguszewski, Milosz; Ghadri, Jelena-Rima; Seifert, Burkhardt; Hiestand, Thierry; Herrera, Paola; Gaemperli, Oliver; Landmesser, Ulf; Maier, Willibald; Nallamothu, Brahmajee K; Windecker, Stephan; Lüscher,

Thomas F; Templin, Christian (2015). Drug-eluting stents vs. bare metal stents in patients with cardiogenic shock: a comparison by propensity score analysis. Journal of Cardiovascular Medicine, 16(3):220-229.
DOI: https://doi.org/10.2459/JCM.0000000000000106

FIC Federazione Italiana di Cardiologia
Italian Federation of Cardiology

Drug-eluting stents vs. bare metal stents in patients with cardiogenic shock: a comparison by propensity score analysis

Milosz Jaguszewski[a,*], Jelena-Rima Ghadri[a,*], Burkhardt Seifert[b], Thierry Hiestand[a], Paola Herrera[a], Oliver Gaemperli[a], Ulf Landmesser[a], Willibald Maier[a], Brahmajee K. Nallamothu[c], Stephan Windecker[d], Thomas F. Lüscher[a] and Christian Templin[a]

Background **In patients with cardiogenic shock, data on the comparative safety and efficacy of drug-eluting stents (DESs) vs. bare metal stents (BMSs) are lacking. We sought to assess the performance of DESs compared with BMSs among patients with cardiogenic shock undergoing percutaneous coronary intervention (PCI).**

Methods **Out of 236 patients with acute coronary syndromes complicated by cardiogenic shock, 203 were included in the final analysis. The primary endpoint included death, and the secondary endpoint of major adverse cardiac and cerebrovascular events (MACCEs) included the composite of death, myocardial infarction, any repeat revascularization and stroke. Patients were followed for a minimum of 30 days and up to 4 years. As stent assignment was not random, we performed a propensity score analysis to minimize potential bias.**

Results **Among patients treated with DESs, there was a lower risk of the primary and secondary endpoints compared with BMSs at 30 days (29 vs. 56%, $P<0.001$; 34 vs. 58%, $P=0.001$, respectively) and during long-term follow-up [hazard ratio 0.43, 95% confidence interval (CI) 0.29–0.65, $P<0.001$; hazard ratio 0.49, 95% CI 0.34–0.71, $P<0.001$, respectively]. After propensity score adjustment, all-cause mortality was reduced among patients treated with DESs compared with BMSs both at 30 days [adjusted odds ratio (OR) 0.26, 95% CI 0.11–0.62; $P=0.002$] and during long-term follow-up (adjusted hazard ratio 0.40, 95% CI 0.22–0.72; $P=0.002$). The rate of MACCE was lower among patients treated with DESs compared with those treated with BMSs at 30 days (adjusted OR 0.42, 95% CI 0.19–0.95; $P=0.036$). The difference in MACCEs between devices approached significance during long-term follow-up (adjusted hazard ratio 0.60, 95% CI 0.34–1.01; $P=0.052$).**

Conclusion **DESs appear to be associated with improved clinical outcomes, including a reduction in all-cause mortality compared with BMSs among patients undergoing PCI for cardiogenic shock, possibly because of a pacification of the infarct-related artery by anti-inflammatory drug. The results of this observational study require confirmation in an appropriately powered randomized trial.**

J Cardiovasc Med 2014, **15**:000–000

Keywords: bare-metal stent, cardiogenic shock, drug-eluting stent, propensity score analysis

[a]University Heart Center, Department of Cardiology, University Hospital Zurich, [b]Division of Biostatistics, ISPM, University Zurich, Zurich, Switzerland, [c]Cardiovascular Center, University of Michigan, Ann Arbor, Michigan, USA and [d]Department of Cardiology, Bern University Hospital, Bern, Switzerland

Correspondence to Christian Templin, MD, PhD, FESC, University Heart Center, Department of Cardiology, University Hospital Zurich, Raemistr. 100, 8091 Zurich, Switzerland
Tel: +41 44 255 9585; fax: +41 44 255 4401; e-mail: christian.templin@usz.ch

Received 25 November 2013 **Revised** 16 March 2014
Accepted 18 March 2014

Introduction

Cardiogenic shock is a life-threatening complication of acute coronary syndromes (ACSs) occurring in approximately 5–10% of patients.[1,2] Indeed, cardiogenic shock is associated with a high mortality ranging between 30 and 80%.[3–5] This poor prognosis is determined in part by the amount of myocardium at risk, the timeliness of revascularization, the use of assist devices (mechanical support), adjunctive medical therapy and the patients' age.[1,6]

Recently, it has been suggested that the type of stent used in primary percutaneous coronary interventions (pPCIs) might impact on outcomes of patients with ACS. Indeed, drug-eluting stents (DESs) reduce neointimal hyperplasia when compared with bare metal stents (BMSs); however, data on the safety and performance of DESs in ACS are limited.[7,8] The Harmonizing Outcomes With Revascularization And Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial suggested that paclitaxel-eluting stents may be used in patients with ST-segment elevation myocardial infarction (STEMI) for improving the outcomes.[7] However, in line with previous smaller randomized clinical trials, the mortality was similar in both BMS and paclitaxel-eluting stent groups.[7] We recently showed in the randomized Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction (COMFORTABLE) AMI trial that

* Dr. Milosz Jaguszewski and Dr. Jelena-Rima Ghadri contributed equally to this work and are shared first authors.

1558-2027 © 2014 Italian Federation of Cardiology DOI:10.2459/JCM.0000000000000106

Copyright © Italian Federation of Cardiology. Unauthorized reproduction of this article is prohibited.

biolimus-eluting stents were superior in terms of major adverse cardiac and cardiovascular events (MACCEs) in patients with ACS compared to BMS.[9] A limitation of both the HORIZONS-AMI trial and the COMFORTABLE AMI trial, however, was the very small number of patients with cardiogenic shock.[7,9]

Therefore, all-comers studies on patients with AMI would be required for determining the true effects of DES implantation compared with BMS on clinical outcomes in high-risk patients. To address the limitations of previously published data, we aimed to compare DES with BMS in patients with cardiogenic shock using a propensity score analysis to adjust for imbalances in baseline characteristics.

Methods

Patient population

Consecutive patients referred for PCI between 1 June 2007 and 1 July 2012 to the University Heart Centre, Department of Cardiology of the University Hospital of Zurich, with the diagnosis of ACS, were included in the Zurich ACS-Registry, of whom 236 were complicated by cardiogenic shock. All patients with cardiogenic shock on admission were considered for enrollment, if at least one DES or BMS had been implanted. Patients were excluded from the present study, if early surgical revascularization or PCI without stent implantation was performed (Fig. 1). Patients who received both DES and BMS were also excluded from the final analysis. All patients included in the final analysis ($n = 203$) were linked to the long-term follow-up. Due to the retrospective nature of this study, the need for informed consent was waived by the institutional review board (local ethics committee, University Hospital Zurich, Switzerland).

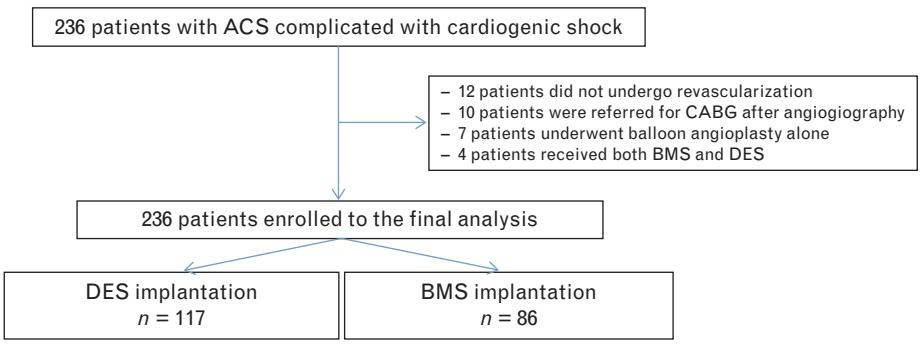
Definitions

The diagnosis of STEMI was based on a new ST-segment elevation of at least 1 mm in two or more contiguous leads or if a new left bundle branch block (LBBB) was identified accompanied with elevated cardiac serum troponin T level above the threshold for myocardial necrosis. Non-ST-segment elevation myocardial infarction (NSTEMI) was defined as the elevation of biomarkers of myocardial necrosis (e.g., troponin) without ST-segment elevation in ECG in the setting of angina. Cardiogenic shock was defined as persistent SBP less than 90 mmHg not responsive to fluid supplementation or the need for vasopressor agents with evidence of pulmonary edema and systemic signs of hypoperfusion.[2] Cardiogenic shock was also considered when preserved SBP was more than 100 mmHg achieved by means of vasopressors or intra-aortic balloon pump (IABP) support.[2] Full revascularization was defined as the complete reperfusion of all ischemic myocardial territories. Areas of old infarction with no viable myocardium was not reperfused during the acute course of ACS.

Procedures

Coronary angiography through the femoral access was performed on an Allura 9 (Philips Healthcare, The Leiden, Netherlands) and an Allura XPER FD10/10 (Philips Medical) catheterization equipment in the Andreas Gruentzig Catheterization Laboratories of the University Hospital of Zurich, Switzerland, following a protocol, which consisted of a biplane angiography of the left coronary artery with two radiation exposures in four orientations and of the right coronary artery with two exposures in two orientations. Additional views were performed at the operator's discretion, if necessary. Two independent cardiologists evaluated coronary stenosis grade, Thrombolysis in Myocardial Infarction (TIMI) grade flow as well as the presence of thrombus. Patients enrolled into the registry received either DES [i.e. PROMUS (Boston Scientific, Natick, Massachusetts, USA), Xience V (Abbott Vascular, Santa Clara, California, USA), Cypher (Cordis Company, Bridgeton, New Jersey, USA), Taxus (Boston Scientific), Biomatrix (Biosensors Europe SA, Morges, Switzerland) or Orsirio (Biotronik SE & Co. KG, Berlin, Germany) or BMS (Multilink by Guidant Corporation, Indianapolis, Indiana, USA); Skylor (INVATEC S.p.A, Roncadelle, Italy); Pro-Kinetic

Fig. 1



Flow chart of the study enrolment. BMS, bare metal stent; CABG, coronary artery bypass grafting; DES, drug-eluting stent.

Copyright © Italian Federation of Cardiology. Unauthorized reproduction of this article is prohibited.

(Biotronik SE & Co. KG) or Driver (Medtronic Vascular, Minneapolis, Minnesota, USA) based on the operator's discretion.

Manual thrombectomy was performed with the use of the Export catheter (Medtronic Inc., Tolochenaz, Switzerland). Intravenous heparin was routinely administered with a minimal dose of 5000 IU or a dose of 70–100 IU/kg to maintain an activated clotting time of greater than 250 s. Dual antiplatelet therapy, including a loading dose of 600 mg of clopidogrel or 60 mg of prasugrel (if not previously on clopidogrel or prasugrel) and 500 mg of acetylsalicylic acid (if not previously on regular aspirin), was provided in all patients before or during the interventional procedure. All patients were expected to continue clopidogrel or prasugrel therapy for at least 12 months after discharge.

The choice of the treatment strategy, including stent type, glycoprotein IIb/IIIa antagonist or bivalirudin administration and thrombectomy catheters' use, was up to the physician's discretion. The operators based this decision on their clinical judgment integrating the visual angiography finding with all available clinical information.

SYNTAX score analysis

SYNTAX score assessment was performed by a cardiologist blinded to the clinical outcomes of the patients using a scoring system for all significant lesions (≥50%) in the vessels 1.5 mm or greater in diameter by applying a dedicated SYNTAX score algorithm. SYNTAX score was calculated using angiography just after the first dilatation of the culprit vessel to include all significant lesions. However, if the culprit vessel was occluded before PCI, the lesion was scored as an acute occlusion with the duration of less than 3 months.

Study endpoints

The primary endpoint of the present study was all-cause mortality, and the secondary endpoint MACCE was the composite of death, myocardial infarction (MI), any repeat revascularization and stroke at 30 days and up to 4 years. We also evaluated the rate of ischemia-driven target lesion revascularization (TLR) and definite stent thrombosis as defined by the ARC criteria. TLR was defined as repeat intervention to treat a luminal diameter stenosis of at least 50% in the stent or within the 5-mm borders proximal or distal to the stent and after the event of angina. Postdischarge observation was obtained as part of our hospital quality assurance using a standardized clinical questionnaire.

Statistical analysis

For statistical analysis, IBM SPSS Statistics 20 (IBM Corp, Armonk, New York, USA) was used. Continuous data were expressed as mean values (±standard deviation) or median with interquartile range and compared using an independent samples *t*-test or the Mann–Whitney *U*-test. Categorical data were reported as proportions and evaluated by the Pearson's χ^2 or the Fisher's exact test, where appropriate. Overall death and MACCEs were analyzed using the Kaplan–Meier time-to-event curves and were compared between DES and BMS using the log-rank test. All tests were two-sided and a $P < 0.05$ was considered as statistically significant.

As an early benefit of DES would be unlikely, we performed a sensitivity analysis for assessing differences between the two stent groups in all-cause mortality and MACCE 2 days after stent placement.

Furthermore, to limit the observational character of the study, we also performed a propensity score analysis. For the computation of the propensity score, the following variables were included into a nonparsimonious logistic regression with DES as dependent variable: age, sex, STEMI on admission, hypertension, diabetes, smoking, hypercholesterolemia, family history, obesity, known stroke, known MI, known coronary artery disease, heart rate, SBP, DBP, left ventricular ejection fraction, out-of-hospital resuscitation, type of cardiac arrest, use of vasopressors, use of IABP, intubation, one-time urgent full revascularization, Global Registry of Acute Coronary Events (GRACE) score risk, use of glycoprotein IIb/IIIa antagonist and use of thrombectomy; angiographic analysis: SYNTAX score, culprit lesion and its segment, TIMI grade flow before PCI, presence of chronic total occlusion and stent length; laboratory values on admission: creatinine, glomerular filtration rate, myoglobin, creatine kinase, creatine kinase-muscle brain type fraction, N-terminal brain-type natriuretic peptide, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, hemoglobin and red blood cells, white blood cells (WBCs); drug administration before presentation: aspirin, clopidogrel, prasugrel, statin, β-blocker, angiotensin-converting enzyme inhibitors, diuretics, sartans, calcium channel blockers and vitamin K antagonists.

Variables with a skewed distribution were logarithmically transformed before analysis. Missing values were replaced by multiple regression imputation for the respective analysis. The model was well calibrated (the Hosmer–Lemeshow test χ^2 8.3, 8 df, $P = 0.40$) and highly discriminating (c-value 0.91). The validity of logistic regression was assessed using the Hosmer–Lemeshow test and proportional hazard in Cox regression was estimated visually. Finally, logistic regressions for 30-day event rates of death and MACCE, and Cox regressions for long-term death and MACCE, respectively, as dependent variables, and DES and the propensity score, divided in quintiles, as independent variables were performed.

Results

Baseline characteristics

Out of 236 patients, 203 patients with cardiogenic shock were included into the final analysis. Of those, 157

Copyright © Italian Federation of Cardiology. Unauthorized reproduction of this article is prohibited.

patients (77%) were admitted with the primary diagnosis of STEMI and 46 patients (23%) with NSTEMI. The mean age of the total study population was 63.9 ± 11.6 years, and 79% ($n = 160$) were men. DESs were implanted in 58% ($n = 117$) and BMSs in 42% ($n = 86$) of all patients. Of the patients treated with DESs, 50% ($n = 59$) received everolimus-eluting stents, 31% ($n = 36$) received zotarolimus-eluting stents and 19% ($n = 22$) received other DESs (biolimus-eluting, paclitaxel-eluting, sirolimus-eluting or tacrolimus-eluting stents). The risk profiles of the two groups of patients treated with DES or BMS implantation were similar (Tables 1 and 2). The mean number of risk factors was 2.2 ± 1.4 and most patients were classified as high risk by GRACE risk score with a mean value for in-hospital death of 266 ± 30.7 (range 164–338) and the composite of death and MI of

Table 1 Baseline characteristics, drug-eluting stent vs. bare metal stent ($n = 203$)

Variable	DES ($n = 117$)	BMS ($n = 86$)	*P* value
Age (years)	62.4 (±11.1)	65.9 (±12.1)	0.02
Female sex	24 (21%)	19 (22%)	0.86
STEMI	91 (78%)	66 (77%)	0.87
NSTEMI	26 (22%)	20 (23%)	0.87
GRACE score			
In-hospital death	266 (±31.1)	266 (±30.3)	0.81
In-hospital death + MI	198 (±26.8)	201 (±25.6)	0.34
6-month death	400 (±48.8)	388 (±54.3)	0.25
6-month death + MI	319 (±36.9)	315 (±40.0)	0.59
Cardiovascular risk factors			
Arterial hypertension	60 (51%)	48 (56%)	0.57
Dyslipidemia	39 (33%)	27 (31%)	0.88
Smoking	58 (50%)	40 (47%)	0.67
Diabetes mellitus	19 (16%)	17 (20%)	0.58
Obesity	26 (22%)	20 (23%)	0.87
Positive family history	34 (29%)	23 (27%)	0.75
Cumulative cvRF	2.2 (±1.4)	2.2 (±1.4)	0.99
Cardiovascular history			
CAD	20 (17%)	12 (14%)	0.57
MI	15 (13%)	8 (9%)	0.51
Stroke	2 (2%)	3 (4%)	0.65
Laboratory values, maximal values			
Creatinine (μmol/l)	122 (94–194)	138 (109–249)	0.05
NT-proBNP (ng/l)	3801 (1459–10746)	5002 (1956–13182)	0.12
WBCs (g/l)	17.6 (13.5–23.0)	19.9 (13.3–22.3)	0.80
hsCRP (ng/l)	160 (66–254)	157 (72–261)	0.77
Myoglobin (μg/l)	2255 (918–4250)	1874 (878–4261)	0.56
Creatine kinase (U/l)	3244 (1348–6355)	1989 (1087–4377)	0.05
hsTnT (μg/l)	7.3 (2.7–14.1)	5.65 (2.1–11.0)	0.09
LDH (U/l)	829 (546–1520)	1527 (830–2487)	0.86
ASPAT (U/l)	432 (188–756)	297 (143–700)	0.38
ALAT (U/l)	136 (86–248)	148 (79–275)	0.50
Hemodynamics			
Heart rate (b.p.m.)	88.6 (±24.8)	88.3 (±25.3)	0.92
SBP (mmHg)	90.5 (±13.3)	88.2 (±16.3)	0.34
DBP (mmHg)	54.9 (±10.1)	53.9 (±12.2)	0.54
LVEF (%)	35.9 (±9.8)	35.9 (±10.4)	0.73
LVEDP (mmHg)	22.5 (±8.1)	23.8 (±7.1)	0.46
IABP	93 (80%)	64 (74%)	0.40
Reanimation	81 (69%)	54 (63%)	0.37
First out-of-hospital REA	68 (58%)	47 (55%)	0.67
First in-hospital REA	15 (13%)	7 (8%)	0.36
Intubation	80 (68%)	61 (71%)	0.76
Ventricle fibrillation as first rhythm	59 (54%)	34 (43%)	0.58
PICCO catheter	8 (7%)	11 (13%)	0.22
Coolguard	33 (28%)	16 (19%)	0.14
Impella/ECMO	3 (3%)	4 (5%)	0.46
Vasopressors	73 (62%)	59 (69%)	0.38
Medication on admission			
Aspirin	39 (34%)	29 (34%)	0.98
Clopidogrel/prasugrel	13 (11%)	9 (11%)	0.88
ACE inhibitor or ARB	19 (17%)	16 (19%)	0.70
β-Blocker	31 (27%)	20 (23%)	0.39
Statin	33 (29%)	20 (23%)	0.55
Diuretic	14 (12%)	12 (14%)	0.68
Calcium blocker	14 (12%)	9 (11%)	0.71

Data are presented as *n* (%) or mean ± standard deviation or median with interquartile range. ACE, angiotensin-converting enzyme; ALAT, alaninaminotransferase; ARB, angiotensin-receptor blocker; ASPAT, aspartate transaminase; BMS, bare metal stent; CAD, coronary artery disease; CK-MB, creatine kinase muscle brain type-isoenzyme; CRP, C-reactive protein; cvRF, cardiovascular risk factors; DES, drug-eluting stent; ECMO, extracorporeal membrane oxygenation; GFR, glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; hsTnT, high sensitive troponin T; IABP, intra-aortic balloon pump; LDH, lactate dehydrogenases; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; pro-BNP, *N*-terminal prohormone brain natriuretic peptide; REA, reanimation; STEMI, ST-segment elevation myocardial infarction; WBCs, white blood cells.

Copyright © Italian Federation of Cardiology. Unauthorized reproduction of this article is prohibited.

Table 2 Angiographic and procedural profile, drug-eluting stent vs. bare metal stent ($n = 203$)

Variable	DES ($n = 117$)	BMS ($n = 86$)	P value
SYNTAX score	30.4 (±16.5)	31.5 (±18.1)	0.69
SYNTAX score ≤22	41 (35%)	28 (33%)	0.71
SYNTAX score 23–32	31 (27%)	23 (27%)	0.97
SYNTAX score 33+	45 (39%)	35 (41%)	0.75
SVD	36 (31%)	19 (22%)	0.17
2-Vessel disease	40 (34%)	28 (33%)	0.81
3-Vessel disease	41 (35%)	39 (45%)	0.14
CTO	36 (31%)	27 (31%)	0.92
Full revascularization	94 (80%)	64 (74%)	0.39
No. of lesions	2.9 (±1.9)	3.5 (±2.1)	0.18
No. of stents implanted	2.1 (±1.3)	1.7 (±0.8)	0.08
Total length implanted	44.4 (±28.1)	36.9 (±19.2)	0.14
Baseline TIMI flow grade 0	94 (80%)	71 (83%)	0.39
TIMI flow grade after PCI			
TIMI flow grade 3	109 (93%)	75 (87%)	0.15
TIMI flow grade ½	6 (5%)	9 (10%)	0.15
TIMI flow grade 0	2 (2%)	2 (2%)	0.75
Thrombectomy	64 (55%)	26 (30%)	0.001
Glycoprotein IIb/IIIa	45 (39%)	22 (26%)	0.07
Culprit lesion			
Left main	10 (9%)	4 (5%)	0.28
LAD	72 (62%)	33 (38%)	0.001
LCX	17 (15%)	11 (13%)	0.72
RCA	12 (10%)	37 (43%)	<0.001
Bypass	6 (5%)	1 (1%)	0.13
Segment			
Ostial/proximal segment	94 (80%)	60 (70%)	0.08
Medial segment	17 (15%)	17 (20%)	0.32
Distal segment	6 (5%)	9 (11%)	0.15

Data are presented as *n* (%) or mean ± SD. BMS, bare metal stent; CTO, chronic total occlusion; DES, drug-eluting stent; LAD, left anterior descending; LCX, left circumflex artery; MVD, multivessel disease; RCA, right coronary artery; SVD, single-vessel disease; TIMI, thrombolysis in myocardial infarction.

199 ± 26.3 (range 111–262). The mean left ventricular ejection fraction was 35.9 ± 10.0% by left ventricle angiography, and the average left ventricular end-diastolic pressure was 23.0 ± 7.7 mmHg. The average Syntax score was 30.8 ± 17.2 with a maximal value of 88. No significant differences were documented between DES and BMS groups in average WBC level on admission (15.8 ± 6.7 vs. 14.9 ± 5.2 g/l, $P = 0.59$) and maximal WBC [17.6 (13.5–23.0) vs. 19.9 (13.3–22.3) g/l, $P = 0.80$]. In addition, mean high-sensitivity C-reactive protein (hsCRP) on admission was similar for both DESs and BMSs (34.8 ± 68.0 vs. 37.7 ± 59.5 ng/l, $P = 0.32$), as well as after maximal hsCRP [DES vs. BMS: 160 (66–254) vs. 157 (72–261) ng/l, $P = 0.77$]. To exclude potential differences in blood values on admission, all laboratory profiles were enclosed into the propensity score analysis. We did not document any significant differences in maximal laboratory values (Table 1). The baseline characteristics of the study population are summarized in Table 1. The angiographic and procedural profile is shown in Table 2.

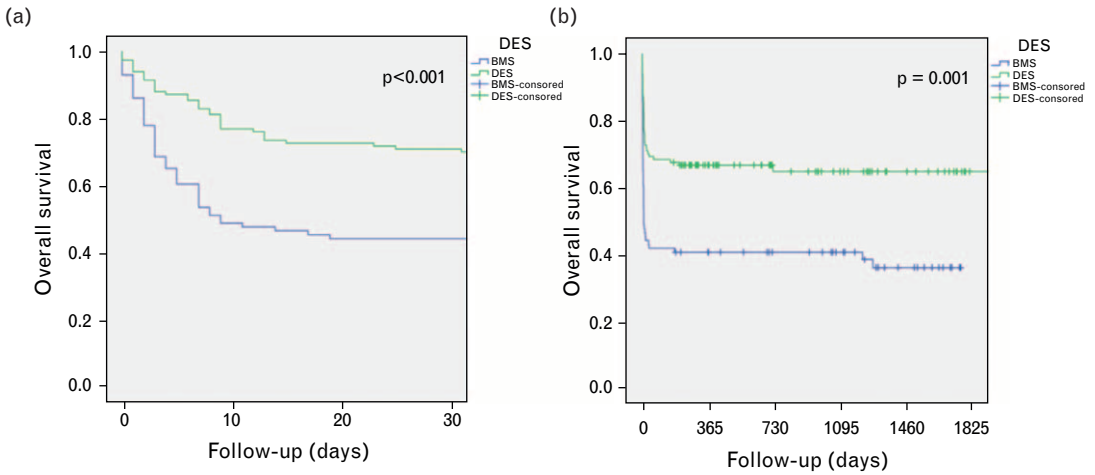
The long-term follow-up averaged 446 ± 589 days for the entire study population (DES vs. BMS: 494 ± 585 vs. 379 ± 592 days, respectively; $P = 0.17$). The mean follow-up of patients who survived 30 days was 790 ± 589 days (DES vs. BMS: 739 ± 577 vs. 900 ± 608 days, respectively; $P = 0.18$).

Glycoprotein IIb/IIIa therapy was administered in 33% of patients ($n = 67$), whereas thrombectomy was performed in 44% ($n = 90$) of patients. None of the patients underwent fibrinolysis before presentation. Full revascularization was documented in 78% ($n = 158$) of patients with a mean stent use of 1.9 ± 1.1 per patient (Table 2). There were no complications related to the passage or deployment of the balloon or stent. In one patient, no reflow phenomenon was observed after BMS implantation.

Clinical outcomes

The overall mortality rate at 30 days was 40% ($n = 82$). In the unadjusted analysis, the primary endpoint of all-cause mortality was significantly lower among patients treated with DESs compared with BMSs at 30 days (29 vs. 56%, $P < 0.001$) (Fig. 2a). Similar findings were obtained

Fig. 2



A 30-day (a) and long-term mortality (b) for patients with drug-eluting stents (DESs) and bare metal stents (BMSs), unadjusted analysis.

Copyright © Italian Federation of Cardiology. Unauthorized reproduction of this article is prohibited.

Table 3 Clinical outcomes, drug-eluting stent vs. bare metal stent ($n = 203$)

	Before adjustment			After propensity score analysis adjustment	
Overall analysis	DES ($n = 117$)	BMS ($n = 86$)	*P*	Adjusted OR (95% CI)	*P*
30-day follow-up					
All-cause death	34 (29%)	48 (56%)	<0.001	0.26 (0.11–0.62)	0.002
Cardiac death	33 (28%)	47 (55%)	<0.001	0.27 (0.11–0.64)	0.003
MACCE	40 (34%)	50 (58%)	0.001	0.42 (0.19–0.95)	0.036
	HR (95% CI)		*P*	Adjusted HR (95% CI)	*P*
Long-term follow-up					
All-cause death	0.43 (0.29–0.65)		<0.001	0.40 (0.22–0.72)	0.002
Cardiac death	0.45 (0.30–0.69)		<0.001	0.41 (0.23–0.76)	0.004
MACCE	0.49 (0.34–0.71)		<0.001	0.60 (0.34–1.01)	0.052
	Before adjustment			After propensity score analysis adjustment	
Sensitivity analysis	HR (95% CI)		*P*	Adjusted HR (95% CI)	*P*
Long-term follow-up					
All-cause death	0.44 (0.27–0.69)		<0.001	0.34 (0.18–0.67)	0.002
Cardiac death	0.46 (0.29–0.74)		0.001	0.36 (0.18–0.71)	0.003
MACCE	0.50 (0.33–0.76)		0.001	0.58 (0.33–1.02)	0.058

BMS, bare metal stent; DES, drug-eluting stent; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular event; OR, odds ratio.

during long-term follow-up [hazard ratio 0.43, 95% confidence interval (CI) 0.29–0.65, $P < 0.001$) (Fig. 2b). Patients treated with DESs showed a better outcome than those receiving BMSs for all-cause mortality, especially at 30 days after the index event. MACCE rate was also lower in patients receiving a DES compared with those receiving a BMS, both at 30 days (34 vs. 58%, $P = 0.001$) and during long-term follow-up (hazard ratio 0.49, 95% CI 0.34–0.71, $P < 0.001$) (Table 3, Fig. 3a and b).

The rate of 30-day definite stent thrombosis was similar in both study populations ($P = 0.14$). Only one case of late stent thrombosis was observed in the DES group. However, the difference in ischemia-driven TLR for DES vs. BMS approached significance at the long-term follow-up (0.8 vs. 6%, respectively; $P = 0.066$) in this setting.

Propensity score analysis ascertainment

After propensity score adjustment, we noticed a significant reduction in all-cause mortality in patients receiving DESs compared with those receiving BMSs both at 30 days [adjusted odds ratio (OR) 0.26, 95% CI 0.11–0.62; $P = 0.002$] and during long-term follow-up [adjusted hazard ratio (AHR) 0.40, 95% CI 0.22–0.72; $P = 0.002$] (Fig. 4a and b). Similarly, there was a significant difference in the rates of MACCE among patients receiving DESs as compared with BMSs in the propensity score adjustment analysis at 30 days (adjusted OR 0.42, 95% CI 0.19–0.95; $P = 0.036$) (Fig. 5a). During long-term follow-up, the difference between DES and BMS groups approached significance with respect to overall MACCE rate (AHR 0.60, 95% CI 0.34–1.01; $P = 0.052$) (Table 3, Fig. 5b).

A sensitivity analysis

The significantly lower event rate for long-term death and MACCE among patients treated with DESs as compared with BMSs remained unchanged after exclusion of all events occurring within the first 2 days after admission (hazard ratio 0.44, 95% CI 0.27–0.69, $P < 0.001$; hazard ratio 0.50, 95% CI 0.33–0.76, $P = 0.001$, respectively). Likewise, after propensity score adjustment, the long-term rates of death and MACCE in the DES group remained lower compared with the BMS group (AHR 0.34, 95% CI 0.18–0.67, $P = 0.002$; AHR 0.58, 95% CI 0.33–1.02, $P = 0.058$, respectively) (Table 3).

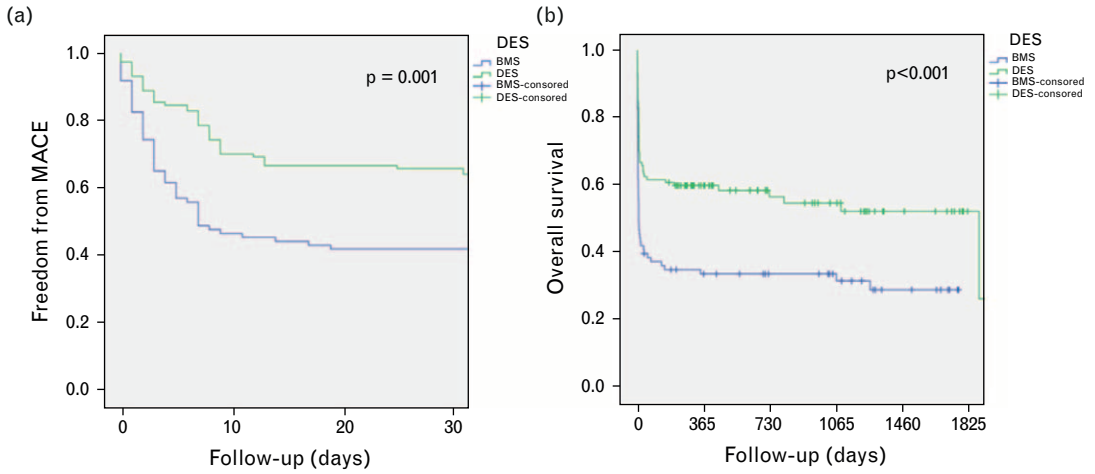
Discussion

This study for the first time suggests that in patients presenting with an ACS and cardiogenic shock, the implantation of DES is associated both with a lower mortality and a lower risk of MACCE as compared with BMS.

In spite of all the progress made in the management of patients with ACS in the last decades, cardiogenic shock remains a severe complication associated with a markedly increased mortality and MACCE rate compared with hemodynamically stable patients.[2] In the present study, the overall 30-day mortality rate was 40%, which is comparable with those in other shock trials.[10,11] In the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock trial and in registry data, mortality varied from 22 up to 88% depending on the presence or absence of clinical predictors, including previous MI and the treatment strategies.[10,11] As expected, early revascularization improved survival rate

Copyright © Italian Federation of Cardiology. Unauthorized reproduction of this article is prohibited.

Fig. 3

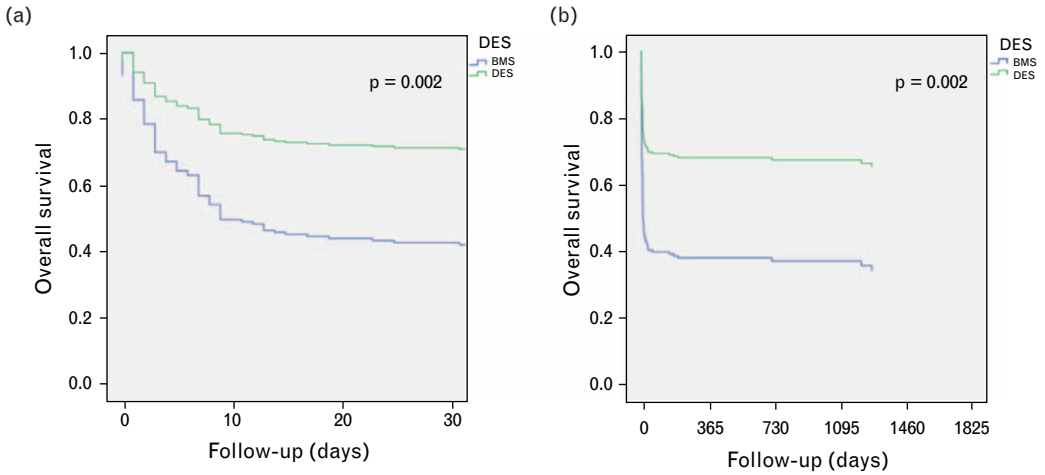


A 30-day (a) and long-term major adverse cardiac and cerebrovascular events (MACCEs) (b) for patients with drug-eluting stents (DESs) and bare metal stents (BMSs), unadjusted analysis.

across a broad range of risk strata.[10,11] In the GRACE registry, fatality rates for cardiogenic shock ranged between 35% for patients receiving revascularization and up to 74% in those not undergoing a pPCI procedure.[4] Indeed, pPCI and coronary stenting are important predictors of in-hospital mortality.[4] Thus, further research is a particular clinical need in this patient population.

So far, it remained unclear whether DES implantation during primary PCI would have a substantial impact on outcomes in patients with cardiogenic shock. Indeed, Champion *et al.*[12] even reported a trend toward a higher mortality after DES implantation. Therefore, they strongly suggested that DES should not be the treatment of choice in this patient population.[12] These findings were surprising, as a substantial reduction in restenosis rate and revascularization has been documented using DES in many trials enrolling patients with stable CAD[13] and in two trials in patients with ACS.[7,9] However, so far, randomized trials in patients with ACS (i.e. HORIZONS-AMI, clinical Evaluation of the Xience-V Stent in Acute Myocardial INfArcTION and COMFORTABLE) enrolled only a low proportion of patients with cardiogenic shock and, thus, they did not address the question, whether DESs indeed are advantageous in ACS patients with hemodynamic compromise or high-risk coronary

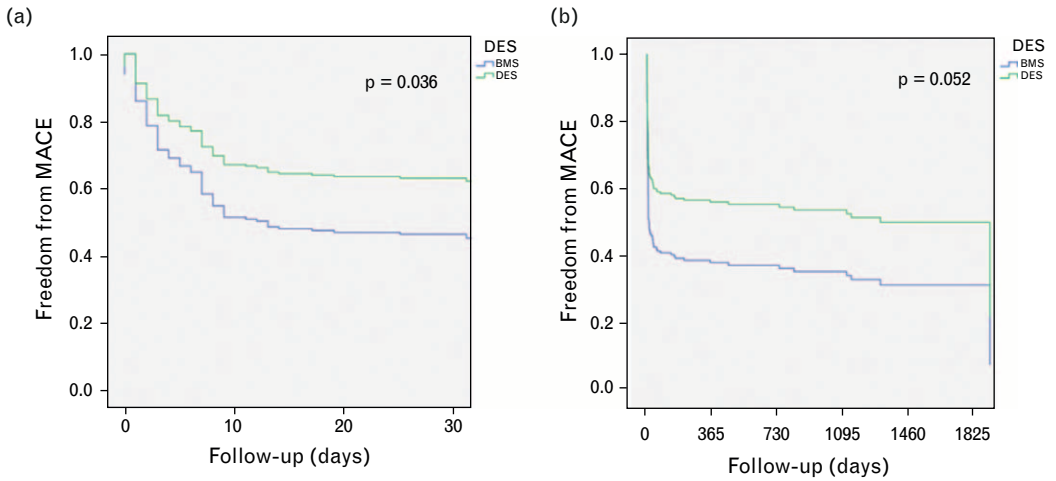
Fig. 4



A 30-day (a) and long-term mortality (b) for patients with drug-eluting stents (DESs) and bare metal stents (BMSs), after propensity score ascertainment.

Copyright © Italian Federation of Cardiology. Unauthorized reproduction of this article is prohibited.

Fig. 5



A 30-day (a) and long-term major adverse cardiac and cerebrovascular events (MACCEs) (b) for patients with drug-eluting stents (DESs) and bare metal stents (BMSs), after propensity score ascertainment.

anatomy.[7,9] Indeed, ACS studies enrolling all-comers documented a markedly higher event rate compared with these randomized trials.[14]

In contrast to previous reports,[15,16] our results based on a markedly larger study population strongly suggest that the use of DESs in patients with cardiogenic shock does indeed provide a substantial survival benefit and a marked reduction in MACCE as compared with BMSs both at 30 days and at long-term follow-up. The majority of patients of this registry would not have been eligible for randomized clinical trials because of their hemodynamic instability, lesion complexity or because of the fact that they had been intubated and/or resuscitated. The clinical and anatomical complexity of the patients is further reflected by their high SYNTAX and GRACE score.[17–19]

As an early benefit of DES implantation appeared unlikely and baseline risk factors could affect the risk of death, we performed a sensitivity analysis, whereby mortality rates were examined 2 days after stent implantation. Importantly, the reduction in long-term MACCE and all-cause mortality with DESs remained significant, indicating the potential for a true benefit of DES in cardiogenic shock. As an operator bias in the selection of BMS in patients with cardiogenic shock and a perceived poor prognosis may have influenced the results, we performed a propensity score analysis to adjust for imbalances. After adjusting for measured confounders, we confirmed a significantly lower rate of 30-day and long-term all-cause mortality and a trend toward a lower rate of MACCE.

The better outcome after DES implantation as compared with BMS in cardiogenic shock at 30 days and during long-term follow-up may be related to the local release of antiproliferative as well as anti-inflammatory agents such as paclitaxel, sirolimus, everolimus, biolimus or zotarolimus, which are known to inhibit inflammation and neointimal proliferation. Indeed, potentially, such anti-inflammatory and immunomodulatory compounds released from DESs may even reduce the production of cytokines such as interleukin-6 and serum amyloid A found at the site of coronary occlusion and in turn affect outcome in these high-risk patients. However, WBC count and hsCRP did not differ in patients receiving a DES or a BMS. Thus, a systemic anti-inflammatory effect of DES is unlikely. However, a local inhibition of the marked inflammatory response at the site of coronary occlusion[20,21] may still be involved, especially early after DES placement when up to 80% of the drug is eluted over 30 days.[22]

Although a reduction in in-stent restenosis has been well documented already with first-generation DESs, a high rate of late stent thrombosis initially gave rise to a lot of concern as to their use in ACS wherein thrombus formation is more common than in stable patients.[23,24] Indeed, a recently published meta-analysis supported the notion of an incremental increase of stent thrombosis over time in patients receiving DESs.[25] However, the majority of randomized clinical trials do not address outcomes beyond 1 year.[9] In line with these observations, the rate of definite stent thrombosis in our study overall tended to be higher in patients receiving a DES compared with those receiving a BMS. However, the differences were not significant. Conceptually, the slightly higher rate of definite stent thrombosis after DES implantation at the 30-day follow-up could be because of technical issues, such as stent malapposition, residual

Copyright © Italian Federation of Cardiology. Unauthorized reproduction of this article is prohibited.

dissections, thrombus compression and/or displacement, thrombus burden and/or longer average stent length in the DES group (Table 2).[24] However, the anticipated increased late stent thrombosis or very late stent thrombosis rate after DES implantation was not observed in our study, although the mean follow-up of 30-day survivors surpassed 2 years in the DES group. This observation is in line with the data of recently published trials, in which second-generation DESs reduced the rate of very late stent thrombosis when compared with first-generation DESs.[26] Of note, based on these results, second-generation DESs were preferentially used by our operations also in ACS patients with cardiogenic shock enrolled into the present registry.

Study limitations

The present study is based on an observational single-center registry. Thus, owing to its observational nature, selection bias, in spite of our attempts to account for them using propensity analysis, cannot be fully excluded. Indeed, patients with diabetes mellitus, hyperlipidemia, hypertension, NSTEMI and multivessel disease may be more likely to be treated with DESs, than those with complex lesions, unstable clinical conditions and perceived bad outcome. However, the risk profiles of the patients receiving DESs and BMSs were similar in this registry. Therefore, we could not identify any bias regarding the selected treatment strategy. In addition, potential bias was further accounted for using propensity score analysis.

Second, it is unclear whether the experience at our hospital would be consistent with that of other institutions where cardiogenic shock may be managed differently. Although we attempted to perform a propensity score adjustment, this approach does not account for unobservable differences (i.e. platelet activity, aspirin resistance among others).[27,28] Moreover, owing to the observational character of the present study, we are not able to provide the accurate time duration of the cardiogenic shock before the PCI, which could additionally influence our results. Furthermore, the majority of DESs were implanted between 2010 and 2012 as compared with 2007 and 2009 (68 vs. 45%, $P < 0.001$). Therefore, the influence of intensive care medicine improvement on the better prognosis after DES implantation cannot be excluded. However, the mean follow-up was similar in both groups. Nevertheless, these additional treatment options remain important considerations in patients with cardiogenic shock. Therefore, future work, in particular prospective randomized trials, is needed in this important area.

Conclusion

Our observation is the first to indicate a survival benefit of DES use in patients with cardiogenic shock. However, owing to the importance of this observation for physicians taking care of patients with cardiogenic shock, this hypothesis should be further tested in a prospective, randomized clinical trial.

Acknowledgements

The study was supported in part by a grant of the Swiss National Science Foundation 'Special Program University Medicine' (SPUM) [Nr. 33CM30–124112/1 to TFL] as well as by a strategic alliance with Pfizer, Inc., New York, USA. Furthermore, the authors received research grants from Eli Lilly, Inc., Indianapolis, IN, USA, AstraZeneca, Zug, Switzerland, Medtronic, Tolochenaz, Switzerland and Biosensors, Lausanne, Switzerland. T.F.L. has received honoraria for consulting with Abbott Vascular, Santa Clara, California, USA, and St Jude Medical, Westford, USA.

None of the authors have a competing financial interest.

References

1 Goldberg RJ, Samad NA, Yarzebski J, *et al.* Temporal trends in cardiogenic shock complicating acute myocardial infarction. *N Engl J Med* 1999; **340**:1162–1168.
2 Westaby S, Kharbanda R, Banning AP. Cardiogenic shock in ACS. Part 1: prediction, presentation and medical therapy. *Nat Rev Cardiol* 2012; **9**:158–171.
3 Babaev A, Frederick PD, Pasta DJ, *et al.* Trends in management and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock. *JAMA* 2005; **294**:448–454.
4 Dauerman HL, Goldberg RJ, White K, *et al.* Revascularization, stenting, and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock. *Am J Cardiol* 2002; **90**:838–842.
5 Hochman JS, Sleeper LA, Webb JG, *et al.* Early revascularization in acute myocardial infarction complicated by cardiogenic shock. Shock investigators. Should we emergently revascularize occluded coronaries for cardiogenic shock. *N Engl J Med* 1999; **341**:625–634.
6 Westaby S, Anastasiadis K, Wieselthaler GM. Cardiogenic shock in ACS. Part 2: role of mechanical circulatory support. *Nat Rev Cardiol* 2012; **9**:195–208.
7 Stone GW, Lansky AJ, Pocock SJ, *et al.* Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. *N Engl J Med* 2009; **360**:1946–1959.
8 Brar SS, Leon MB, Stone GW, *et al.* Use of drug-eluting stents in acute myocardial infarction: a systematic review and meta-analysis. *J Am Coll Cardiol* 2009; **53**:1677–1689.
9 Raber L, Kelbaek H, Ostoijc M, *et al.* Effect of biolimus-eluting stents with biodegradable polymer vs bare-metal stents on cardiovascular events among patients with acute myocardial infarction: the comfortable AMI randomized trial. *JAMA* 2012; **308**:777–787.
10 Sleeper LA, Reynolds HR, White HD, *et al.* A severity scoring system for risk assessment of patients with cardiogenic shock: a report from the shock trial and registry. *Am Heart J* 2010; **160**:443–450.
11 Hochman JS, Sleeper LA, Webb JG, *et al.* Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. *JAMA* 2006; **295**:2511–2515.
12 Champion S, Gauzere BA, Lefor Y. Drug-eluting stents should not be used in ST-elevated myocardial infarction with cardiogenic shock. *Arch Intern Med* 2012; **172**:1613–1614.
13 Kaiser C, Galatius S, Erne P, *et al.* Drug-eluting versus bare-metal stents in large coronary arteries. *N Engl J Med* 2010; **363**:2310–2319.
14 de Boer SP, Lenzen MJ, Oemrawsingh RM, *et al.* Evaluating the 'all-comers' design: a comparison of participants in two 'all-comers' PCI trials with nonparticipants. *Eur Heart J* 2011; **32**:2161–2167.
15 Sigwart U. Drug-eluting stents are safe and effective: right or wrong? *J Am Coll Cardiol* 2006; **47**:1361–1362.
16 Colombo A, Corbett SJ. Drug-eluting stent thrombosis: increasingly recognized but too frequently overemphasized. *J Am Coll Cardiol* 2006; **48**:203–205.
17 Lee TH, Hillis LD, Nabel EG. CABG vs. stenting: clinical implications of the SYNTAX trial. *N Engl J Med* 2009; **360**:e10.

Copyright © Italian Federation of Cardiology. Unauthorized reproduction of this article is prohibited.

18 Eagle KA, Lim MJ, Dabbous OH, *et al.* A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA* 2004; **291**:2727–2733.
19 Palmerini T, Genereux P, Caixeta A, *et al.* Prognostic value of the SYNTAX score in patients with acute coronary syndromes undergoing percutaneous coronary intervention: analysis from the ACUITY (acute catheterization and urgent intervention triage strategy) trial. *J Am Coll Cardiol* 2011; **57**:2389–2397.
20 Maier W, Altwegg LA, Corti R, *et al.* Inflammatory markers at the site of ruptured plaque in acute myocardial infarction: locally increased interleukin-6 and serum amyloid A but decreased C-reactive protein. *Circulation* 2005; **111**:1355–1361.
21 Wyss CA, Neidhart M, Altwegg L, *et al.* Cellular actors, Toll-like receptors, and local cytokine profile in acute coronary syndromes. *Eur Heart J* 2010; **31**:1457–1469.
22 Okamura T, Onuma Y, Garcia-Garcia HM, *et al.* 3-dimensional optical coherence tomography assessment of jailed side branches by bioresorbable vascular scaffolds: a proposal for classification. *JACC Cardiovasc Interv* 2010; **3**:836–844.
23 Daemen J, Wenaweser P, Tsuchida K, *et al.* Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet* 2007; **369**:667–678.
24 Sianos G, Papafaklis MI, Daemen J, *et al.* Angiographic stent thrombosis after routine use of drug-eluting stents in ST-segment elevation myocardial infarction: the importance of thrombus burden. *J Am Coll Cardiol* 2007; **50**:573–583.
25 Kalesan B, Pilgrim T, Heinimann K, *et al.* Comparison of drug-eluting stents with bare metal stents in patients with ST-segment elevation myocardial infarction. *Eur Heart J* 2012; **33**:977–987.
26 Stefanini GG, Kalesan B, Serruys PW, *et al.* Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents vs. durable polymer sirolimus-eluting stents in patients with coronary artery disease (leaders): 4 year follow-up of a randomised noninferiority trial. *Lancet* 2011; **378**:1940–1948.
27 Simon T, Verstuyft C, Mary-Krause M, *et al.* Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med* 2009; **360**:363–375.
28 Bradbury J. Aspirin resistance may increase death risk in some patients with heart disease. *Lancet* 2002; **359**:1128.

Copyright © Italian Federation of Cardiology. Unauthorized reproduction of this article is prohibited.